CLIMARA PRO - estradiol and levonorgestrel patch
Bayer HealthCare Pharmaceuticals Inc.

PRESCRIBING INFORMATION

Climara Pro®
(Estradiol/Levonorgestrel Transdermal System)
Rx only

WARNINGS

Estrogens and progestins should not be used for the prevention of cardiovascular disease or dementia. (See WARNINGS, Cardiovascular disorders and Dementia.)
The Women's Health Initiative (WHI) study reported increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombosis in postmenopausal women (50 to 79 years of age) during 5 years of treatment with oral conjugated estrogens (CE 0.625 mg) combined with medroxyprogesterone acetate (MPA 2.5 mg) relative to placebo. (See CLINICAL STUDIES and WARNINGS, Cardiovascular disorders and Malignant neoplasms, Breast cancer.)
The WHI study reported increased risks of stroke and deep vein thrombosis in postmenopausal women (50 to 79 years of age) during 6.8 years of treatment with oral conjugated estrogens (CE 0.625 mg) relative to placebo. (See CLINICAL STUDIES and WARNINGS, Cardiovascular disorders.)
The Women's Health Initiative Memory Study (WHIMS), a substudy of WHI, reported increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4 years of treatment with CE 0.625 mg combined with MPA 2.5 mg and during 5.2 years of treatment with CE 0.625 mg alone, relative to placebo. It is unknown whether this finding applies to younger postmenopausal women. (See CLINICAL STUDIES, WARNINGS, Dementia and PRECAUTIONS, Geriatric Use.)
Other doses of oral conjugated estrogens with medroxyprogesterone acetate, and other combinations and dosage forms of estrogens and progestins were not studied in the WHI clinical trials and, in the absence of comparable data, these risks should be assumed to be similar. Because of these risks, estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

DESCRIPTION

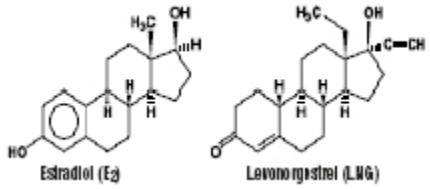
Climara Pro® (Estradiol/Levonorgestrel Transdermal System) is an adhesive-based matrix transdermal patch designed to release both estradiol and levonorgestrel, a progestational agent, continuously upon application to intact skin.

The 22 cm^2 Climara Pro system contains 4.4 mg estradiol and 1.39 mg levonorgestrel and provides a nominal delivery rate (mg per day) of 0.045 estradiol and 0.015 levonorgestrel.

Estradiol USP has a molecular weight of 272.39 and the molecular formula is $C_{18}H_{24}O_2$.

Levonorgestrel USP has a molecular weight of 312.4 and a molecular formula of $C_{21}H_{28}O_2$.

The structural formulas for estradiol and levonorgestrel are:



The Climara Pro system comprises 3 layers. Proceeding from the visible surface towards the surface attached to the skin, these layers are (1) a translucent polyethylene backing film, (2) an acrylate adhesive matrix containing estradiol and levonorgestrel, and (3) a protective liner of either siliconized or fluoropolymer coated polyester film. The protective liner is attached to the adhesive surface and must be removed before the system can be used.

The active components of the system are estradiol and levonorgestrel. The remaining components of the system (acrylate copolymer adhesive and polyvinylpyrrolidone/vinyl acetate copolymer) are pharmacologically inactive.

CLINICAL PHARMACOLOGY

Endogenous estrogens are largely responsible for the development and maintenance of the female reproductive system and secondary sexual characteristics. Although circulating estrogens exist in a dynamic equilibrium of metabolic interconversions, estradiol is the principal intracellular human estrogen and is substantially more potent than its metabolites, estrone and estriol at the receptor level.

The primary source of estrogen in normally cycling adult women is the ovarian follicle, which secretes 70 to 500 mcg of estradiol daily, depending on the phase of the menstrual cycle. After menopause, most endogenous estrogen is produced by conversion of androstenedione, secreted by the adrenal cortex, to estrone by peripheral tissues. Thus, estrone and the sulfate conjugated form, estrone sulfate, are the most abundant circulating estrogens in postmenopausal women.
Estrogens act through binding to nuclear receptors in estrogen-responsive tissues. To date, two estrogen receptors have been identified. These vary in proportion from tissue to tissue.
Circulating estrogens modulate the pituitary secretion of the gonadotropins, luteinizing hormone (LH) and follicle stimulating hormone (FSH), through a negative feedback mechanism. Estrogens act to reduce the elevated levels of these hormones seen in postmenopausal women.
Levonorgestrel inhibits gonadotropin production resulting in retardation of follicular growth and inhibition of ovulation.
Studies to assess the potency of progestins using estrogen-primed postmenopausal endometrial biochemistry and morphologic features have shown that levonorgestrel counteracts the proliferative effects of estrogens on the endometrium.

A. Absorption
Administration of Climara Pro to postmenopausal women produces mean maximum estradiol concentrations in serum in about 2 to 2.5 days. Estradiol concentrations equivalent to the normal ranges observed at the early follicular phase in premenopausal women are achieved within 12-24 hours after the first application.
In one study, steady state estradiol concentrations in serum were measured during week 4 in 44 healthy, postmenopausal women during four consecutive Climara Pro applications of two formulations (0.045 mg estradiol/0.03 mg levonorgestrel and 0.045 mg estradiol/0.015 mg levonorgestrel) to the abdomen (each dose was applied for four 7-day periods). Both formulations were bioequivalent in terms of estradiol and estrone C_{max} and AUC parameters. A summary of Climara Pro single and multiple applications estradiol, estrone and levonorgestrel pharmacokinetic parameters is shown in **Table 1**.
Table 1: Summary of Mean Pharmacokinetic Parameters

Summary of Mean (± SD) Pharmacokinetic Parameters Following a Single Application of Climara Pro in 24 Healthy Postmenopausal Women				
Parameter	**Units**	**Estradiol**	**Estrone**	**Levonorgestrel**
Single application Week 1 Data				
C_{ave}	Pg/mL	37.7 ± 10.4	41 ± 15	136 ± 52.7
C_{max}	Pg/mL	54.3 ± 18.9	43.9 ± 14.9	138 ± 51.8
T_{max}	Hours	42	84	90
C_{min}	Pg/mL	27.2 ± 7.66	32.6 ± 14.3	110 ± 41.7
AUC	Pg.h/mL	6340 ± 1740	6890 ± 2520	22900 ± 8860
Summary of Mean (± SD) Pharmacokinetic Parameters (Week 4) Following Four Consecutive Weekly Applications of Climara Pro in 44 Healthy Postmenopausal Women				
Multiple application Week 4 Data				
C_{ave}	Pg/mL	35.7 ± 11.4	45.5 ± 62.6	166 ± 97.8
C_{max}	Pg/mL	50.7 ± 28.6	81.6 ± 252	194 ± 111
T_{max}	Hours	36	48	48
C_{min}	Pg/mL	33.8 ± 28.7	72.5 ± 253	153 ± 69.6
AUC	Pg.h/mL	6002 ± 1919	7642 ± 10518	27948 ± 16426
All mean parameters are arithmetic means except Tmax which is expressed as the median.				

At steady state, Climara Pro maintains during the application period an average serum estradiol concentration of 35.7 pg/mL as depicted in **Figure 1**.

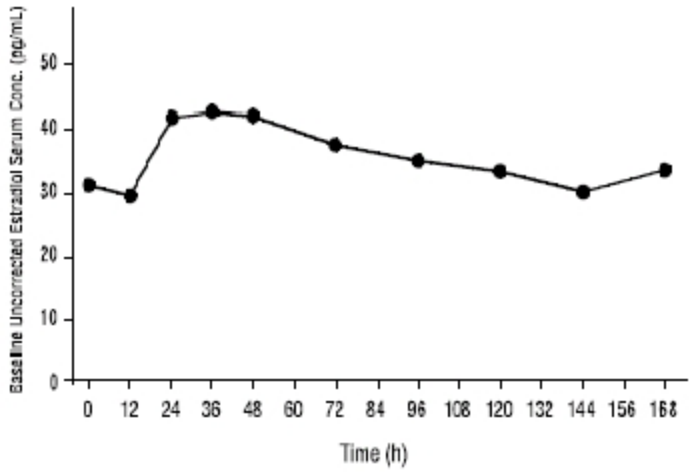


Figure 1: Mean Estradiol Concentration Profile (Week 4) Following Four Consecutive Weekly Applications of Climara Pro

Following the application of the Climara Pro transdermal system, levonorgestrel concentrations are maximum in about 2.5 days. At steady state, Climara Pro maintains during the application period an average serum levonorgestrel concentration of 166 pg/mL as depicted in Figure 2. The mean levonorgestrel pharmacokinetic parameters of Climara Pro are summarized in **Table 1**.

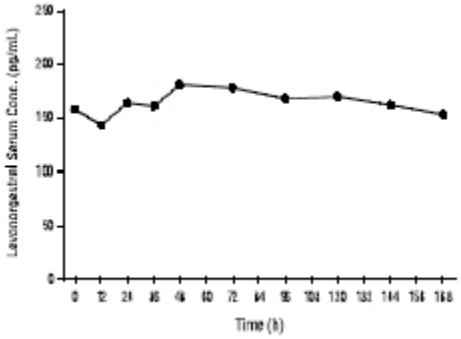


Figure 2: Mean Levonorgestrel Concentration Profile (Week 4) Following Four Consecutive Weekly Applications of Climara Pro

B. Distribution

The distribution of exogenous estrogens is similar to that of endogenous estrogens. Estrogens are widely distributed in the body and are generally found in higher concentrations in the sex hormone target organs. Estrogens circulate in the blood largely bound to sex hormone binding globulin (SHBG) and albumin.

Levonorgestrel in serum is bound to both SHBG and albumin. Following four consecutive weekly applications of Climara Pro mean (± SD) SHBG concentrations declined from a predose value of 47.5 (25.8) to 41.2 (22.4) nmol/L at week 4.

C. Metabolism

Exogenous estrogens are metabolized in the same manner as endogenous estrogens. Circulating estrogens exist in a dynamic equilibrium of metabolic interconversions. These transformations take place mainly in the liver. Estradiol is converted reversibly to estrone, and both can be converted to estriol, which is the major urinary metabolite. Estrogens also undergo enterohepatic recirculation via sulfate and glucuronide conjugation in the liver, biliary secretion of conjugates into the intestine, and hydrolysis in the intestine followed by reabsorption. In postmenopausal women, a significant proportion of the circulating estrogens exist as sulfate conjugates, especially estrone sulfate, which serves as a circulating reservoir for the formation of more active estrogens.

The most important metabolic pathway for levonorgestrel occurs in the reduction of the Δ4- and the 3-oxo-group as well as hydroxylations at positions 2α , 1β, and 16β, followed by conjugation. Most of the metabolites that circulate in the blood are sulfates of 3α , 5β -tetrahydro-levonorgestrel, while excretion occurs predominantly in the form of glucuronides. Some of the parent levonorgestrel also circulates as the 17β-sulfate. *In-vitro* studies on the biotransformation of levonorgestrel in human skin did not indicate any significant metabolism of levonorgestrel during skin penetration.

D. Excretion

Estradiol, estrone, and estriol are excreted in the urine along with glucuronide and sulfate conjugates. Following patch removal, serum estradiol concentrations decline rapidly with a mean (± SD) terminal half-life of 3 ± 0.67 hours.

Levonorgestrel and its metabolites are primarily excreted in the urine. Mean (± SD) terminal half-life for levonorgestrel was determined to be 28 ± 6.4 hours.

E. Special Populations
Climara Pro has been studied only in healthy postmenopausal women.

F. Drug Interactions
In vitro and *in vivo* studies have shown that estrogens are metabolized partially by cytochrome P450 3A4 (CYP3A4). Therefore, inducers or inhibitors of CYP3A4 may affect estrogen drug metabolism. Inducers of CYP3A4 such as St. John's Wort preparations (Hypericum perforatum), phenobarbital, carbamazepine, and rifampin may reduce plasma concentrations of estrogens, possibly resulting in a decrease in therapeutic effects and/or changes in the uterine bleeding profile. Inhibitors of CYP3A4 such as erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir and grapefruit juice may increase plasma concentrations of estrogens and may result in side effects.
Hydroxylation of levonorgestrel is a conversion step which is mediated by cytochrome P450 enzymes. Based on in-vitro and in-vivo studies, it can be assumed that CYP3A, CYP2E and CYP2C are involved in the metabolism of levonorgestrel. Likewise, inducers or inhibitors of these enzymes may either, respectively, decrease the therapeutic effects or result in side effects.

G. Adhesion
A study of the adhesion potential of Climara Pro was conducted in 104 healthy women of 45-75 years of age. Each woman applied a placebo patch, containing only the Climara Pro adhesive without active ingredient, to the upper outer abdominal areas weekly for three weeks. The adhesion assessment was done visually on Days 2, 4, 5, 6 and 7 of each of the three weeks using a four-point scale. The mean scores ranked in the highest category possible on the 0 to 4 scale demonstrating clinically acceptable adhesion performance.

CLINICAL STUDIES

Effects on vasomotor symptoms
The efficacy of 0.045 mg estradiol/0.03 mg levonorgestrel administered weekly versus placebo in the relief of moderate to severe vasomotor symptoms in postmenopausal women was studied in one 12-week clinical trial (n=183, average age 52.1 ± 4.93, 82% Caucasian). The 0.045 mg estradiol/0.03 mg levonorgestrel dosage strength was shown to be statistically better than placebo at weeks 4 and 12 for relief of both the number and severity of moderate to severe hot flushes. See Tables 2 and 3. Climara Pro and the 0.045 mg estradiol/0.03 mg levonorgestrel dosage strength are bioequivalent in terms of estradiol delivery. (See CLINICAL PHARMACOLOGY, Absorption)

Table 2: Summary of Mean Daily Number of Moderate to Severe Hot Flushes-ITT*

		Baseline†	Week 4	Week 8	Week 12
Placebo	n‡	88	82	73	69
	Mean (SD)§	10.8 (5.803)	6.13 (4.311)	5.35 (4.095)	5.59 (4.93)
	Mean Change from baseline (SD)	NA	-4.23 (4.374)	-4.80 (4.448)	-4.55 (5.407)
0.045/.03	n‡	92	88	80	73
	Mean (SD)§	10.13 (3.945)	2.69 (4.455)	1.22 (2.804)	1.06 (3.187)
	Mean Change from baseline (SD)§	NA	-7.40 (4.715)	-8.68 (4.715)	-8.82 (4.336)
p-Value ¶		NA	<0.001#	NA	<0.001#

*****ITT= Intent to –Treat population
† A subject was included at baseline only if the subject had a post-baseline mean score. The post-baseline mean score required 3 days in one week.
‡n= Number of subjects in a treatment group in a cycle; Number of subjects varied from cycle to cycle due to missing data
§SD= standard deviation
¶ p-Value for comparison to placebo, adjusted by the method of Bonferroni
p <0.025

Table 3: Summary of Mean Severity of Moderate to Severe Hot Flushes-ITT

		Baseline*	Week 4 (day 7)	Week 8 (day 7)	Week 12 (day 7)
Placebo	n	89	76	68	57
	Mean (SD)	2.42 (0.282)	1.99 (0.875)	1.93 (0.955)	1.8 (1.034)

	Mean Change from baseline (SD)	NA	-0.4 (0.865)	-0.48 (0.922)	-0.57 (1.044)
0.045/.03	n	92	83	72	55
	Mean (SD)	2.48 (0.295)	1.1 (1.191)	0.82 (1.226)	0.44 (0.96)
	Mean Change from baseline (SD)	NA	-1.4 (1.164)	-1.67 (1.245)	-2.06 (1.005)
p-Value †		NA	<0.001 [*]	NA	<0.001[*]

ITT= Intent to Treat population; n= Number of subjects in a treatment group in a cycle; SD= standard deviation
Severity scores are : 1 = Mild, 2 = Moderate, 3 = Severe. Mean severity of hot flushes by day is [(2X number of moderate hot flushes) + (3X number of severe hot flushes)] / total number of moderate to severe hot flushes on that day. If no moderate to severe hot flush was indicated, the mean severity was 0.
Number of subjects varied from cycle to cycle due to missing data

*****A subject was included at baseline only if the subject had at least 1 post-baseline value.
†p-Value for comparison to placebo, adjusted by the method of Bonferroni; [*] p <0.025

Effects on the endometrium

In a 1-year clinical trial of 412 postmenopausal women (with intact uteri) treated with a continuous regimen of Climara Pro or with an continuous estradiol-only transdermal system, results of evaluable endometrial biopsies show that no hyperplasia was seen with Climara Pro. **Table 4** below summarizes these results (Intent-to-Treat populations).

Table 4: Incidence of Endometrial Hyperplasia during Continuous Combined treatment with Climara Pro, Intent-to-Treat Population

	Climara Pro E_2 0.045mg / LNG 0.015 mg	Estradiol E_2 0.045 mg
	n* = 210	n* = 202
No. of Patients with Biopsies at ≥6 months†	124	139
No. of Patients with Biopsies at 1 year ‡	102	110
No. (%) of Patients with Hyperplasia §	0 (0%) ¶	19 (17.3%)
95% Confidence Interval	0 - 3.55%	9.75 - 24.79%

*****N = number of intent-to-treat subjects
† Defined as at least 180 days of treatment
‡ Defined as ≥ 323 days of treatment
§Includes hyperplasia occurring at any time after initiation of treatment as a proportion of patients with biopsies at 1 year
¶p < 0.0167 P-value for comparison to unopposed estradiol dose using the Fisher Exact test. P-values were adjusted by the method of Bonferroni.

Effects on uterine bleeding or spotting

The effects of Climara Pro on uterine bleeding or spotting, as recorded using an interactive voice response system, were evaluated in one 12-month clinical trial. Results are shown in **Figure 3.**

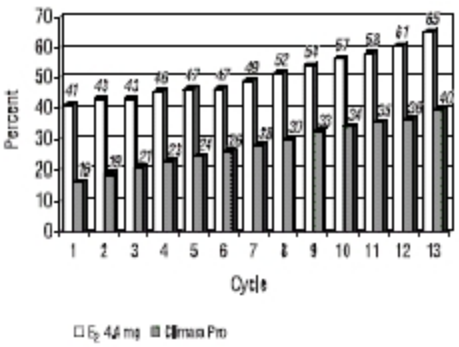


Figure 3: Cumulative proportion of subjects at each cycle with no bleeding/ spotting through the end of cycle 13 Last Observation Carried Forward

Percent based upon the number of subjects with data
Last non-missing cycle carried forward through cycle 13
Bleeding associated with endometrial biopsies not included

Effects on bone mineral density

The effects on bone mineral density (BMD) were studied in a randomized, double-blind, placebo-controlled clinical trial of transdermal systems (patches) containing only estradiol (E2). The patients were postmenopausal women with hysterectomies, 40-83 years of age (mean=51.4 years), and 77.3% Caucasian. Patients received calcium supplements if they appeared deficient on a questionnaire. Vitamin D supplements were not given.

A total of 154 patients were randomized in a 2:2:3 ratio to weekly application of 22 cm^2 patches containing 2.2 mg E2, 4.4 mg E2, or placebo, for 728 days of continuous treatment (26 28-day cycles). Only the results for the estradiol dose in Climara Pro (4.4 mg E2) and for placebo are presented.

Statistically significant increases in the primary efficacy variable, BMD of the lumbar spine (A-P view, L2- L4), were seen for 4.4 mg E2 compared to placebo (see Table 5 and Figure 4). BMD was also measured at the hip (total, non-dominant side) and radius (midshaft, non-dominant side) with statistically significant treatment effects only observed for the hip (see Table 5).

Table 5: Mean Bone Mineral Density (Standard Deviation)*

	4.4 mg E2†	Placebo
Total Lumbar Spine Baseline (g/cm^2)	n=36 1.1 (0.2)	n=46 1.1 (0.2)
% Change from baseline LOCF‡	+1.7% (4.4)	-2.9% (3.8)
P-value compared to placebo	<0.0001	
Total Hip Baseline (g/cm^2)	n=36 0.97 (0.1)	n=48 0.94 (0.1)
% Change from baseline LOCF‡	+1.3% (4.2)	-0.9% (5.2)
P-value compared to placebo	0.05	

*****Intent-to-treat population with on-treatment efficacy data
†E2=estradiol
‡LOCF=Last Observation Carried Forward

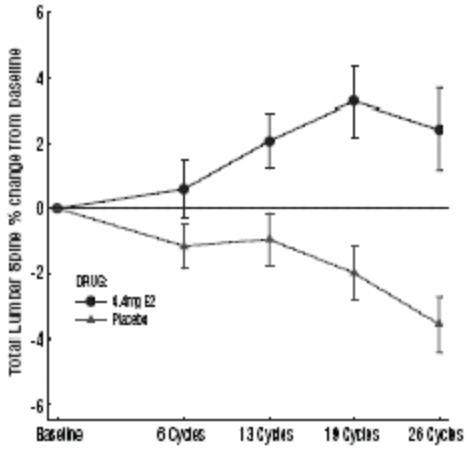


Figure 4: Percent Change From Baseline in Bone Mineral Density (g/cm2) of Lumbar Spine (A-P View, L2–L4) by Treatment Group and Cycle (Mean ± SE)*

* Data in the figure is for 21 patients on 4.4 mg E2 and 27 placebo patients who completed the study; approximately 44% of randomized patients.
The lumbar spine BMD data were analyzed according to baseline estradiol levels. Estimated treatment effects for 4.4 mg E2 were approximately twice as large in the subgroup with baseline estradiol levels <5 pg/mL as in the subgroup with baseline estradiol levels ≥ 5 pg/mL.

Women's Health Initiative Studies
The Women's Health Initiative (WHI) enrolled a total of 27,000 predominantly healthy postmenopausal women to assess the risks and benefits of either the use of oral conjugated estrogens (CE 0.625 mg) alone per day or the use of oral conjugated estrogens (CE 0.625 mg) plus medroxyprogesterone acetate (MPA 2.5 mg) per day compared to placebo in the prevention of certain chronic diseases. The primary endpoint was the incidence of coronary heart disease (CHD) (nonfatal myocardial infarction and CHD death), with invasive breast cancer as the primary adverse outcome studied. A "global index" included the earliest occurrence of CHD, invasive breast cancer, stroke, pulmonary embolism (PE), endometrial cancer, colorectal cancer, hip fracture, or death due to other cause. The study did not evaluate the effects of CE or CE/MPA on menopausal symptoms.
The CE/MPA substudy was stopped early because, according to the predefined stopping rule, the increased risk of breast cancer and cardiovascular events exceeded the specified benefits included in the "global index." Results of the CE/MPA substudy, which included 16,608 women (average age of 63 years, range 50 to 79; 83.9% White, 6.5% Black, 5.5% Hispanic), after an average follow-up of 5.2 years are presented in **Table 6** :

Table 6: RELATIVE AND ABSOLUTE RISK SEEN IN THE CE/MPA SUBSTUDY OF WHI*

Event†	Relative Risk CE/MPA vs placebo at 5.2 Years (95% CI‡)	CE/MPA n = 8,506	Placebo n = 8,102
		Absolute Risk per 10,000 Women-Years	
CHD events	1.29 (1.02-1.63)	37	30
Non-fatal MI	*1.32 (1.02-1.72)*	*30*	*23*
CHD death	*1.18 (0.7-1.97)*	*7*	*6*
Invasive breast cancer§	1.26 (1-1.59)	38	30
Stroke	1.41 (1.07-1.85)	29	21
Pulmonary embolism	2.13 (1.39-3.25)	16	8
Colorectal cancer	0.63 (0.43-0.92)	10	16
Endometrial cancer	0.83 (0.47-1.47)	5	6
Hip fracture	0.66 (0.45-0.98)	10	15
Death due to causes other than the events above	0.92 (0.74-1.14)	37	40
Global Index†	1.15 (1.03-1.28)	170	151
Deep vein thrombosis¶	2.07 (1.49-2.87)	26	13

Vertebral fractures[¶]	0.66 (0.44-0.98)	9	15
Other osteoporotic fractures [¶]	0.77 (0.69-0.86)	131	170

***** Adapted from JAMA, 2002; 288:321-333
† A subset of the events was combined in a "global index", defined as the earliest occurrence of CHD events, invasive breast cancer, stroke, pulmonary embolism, endometrial cancer, colorectal cancer, hip fracture, or death due to other causes
‡Nominal confidence intervals unadjusted for multiple looks and multiple comparisons
§Includes metastatic and non-metastatic breast cancer with the exception of in situ breast cancer
¶ Not included in global index

For those outcomes included in the WHI "global index", the absolute excess risks per 10,000 women-years in the group treated with CE/MPA were 7 more CHD events, 8 more strokes, 8 more PEs, and 8 more invasive breast cancers, while absolute risk reductions per 10,000 women-years were 6 fewer colorectal cancers and 5 fewer hip fractures. The absolute excess risk of events included in the "global index" was 19 per 10,000 women-years. There was no difference between the groups in terms of all-cause mortality. (See WARNINGS, WARNINGS, and PRECAUTIONS.)
The estrogen-alone substudy was stopped early because an increased risk of stroke was observed. Results of the estrogen-alone substudy, which included 10,739 women (average age of 63 years, range 50 to 79; 75.3 percent white, 15 percent black, 6.1 percent Hispanic), after an average follow-up of 6.8 years are presented in Table 7.

Table 7. RELATIVE AND ABSOLUTE RISK SEEN IN THE ESTROGEN-ALONE SUBSTUDY OF WHI[*]

Event[†]	Relative Risk[‡] CE vs. Placebo at 6.8 Years (95% CI)	CE n = 5,310	Placebo n = 5,429
		Absolute Risk per 10,000 Women-years	
CHD events	0.91 (0.75-1.12)	49	54
Non-fatal MI	*0.89 (0.70-1.12)*	*37*	*41*
CHD death	*0.94 (0.65-1.36)*	*15*	*16*
Invasive breast cancer	0.77 (0.59-1.01)	26	33
Stroke	1.39 (1.1-1.77)	44	32
Pulmonary embolism	1.34 (0.87-2.06)	13	10
Colorectal cancer	1.08 (0.75-1.55)	17	16
Hip fracture	0.61 (0.41-0.91)	11	17
Death due to causes other than the events above	1.08 (0.88-1.32)	53	50
Global index[§]	1.01 (0.91-1.12)	192	190
Deep vein thrombosis[†]	1.47 (1.04-2.08)	21	15
Vertebral fractures[†]	0.62 (0.42-0.93)	11	17
Total fractures[†]	0.7 (0.63-0.79)	139	195

*****Adapted from JAMA, 2004; 291:1701-1712
†Not included in global index
‡ Nominal confidence intervals unadjusted for multiple looks and multiple comparisons
§ A subset of the events was combined in a "global index," defined as the earliest occurrence of CHD events, invasive breast cancer, stroke, pulmonary embolism, endometrial cancer, colorectal cancer, hip fracture, or death due to other causes

For those outcomes included in the WHI "global index" that reached statistical significance, the absolute excess risk per 10,000 women-years in the group treated with CE 0.625 mg alone was 12 more strokes, while the absolute risk reduction per 10,000 women-years was 6 fewer hip fractures. The absolute excess risk of events included in the "global index" was a nonsignificant 2 events per 10,000 women-years. There was no difference between the groups in terms of all-cause mortality. (See BOXED WARNINGS, WARNINGS, and PRECAUTIONS.)

Women's Health Initiative Memory Study

The estrogen plus progestin Women's Health Initiative Memory Study (WHIMS), a substudy of WHI, enrolled 4,532 predominantly healthy postmenopausal women 65 years of age and older (47 percent were age 65 to 69 years, 35 percent were 70 to 74 years, and 18 percent were 75 years of age and older) to evaluate the effects of conjugated estrogens (CE 0.625 mg) plus medroxyprogesterone acetate (MPA 2.5 mg) on the incidence of probable dementia (primary outcome) compared with placebo.

After an average follow-up of 4 years, 40 women in the estrogen/progestin group (45 per 10,000 women-years) and 21 in the placebo group (22 per 10,000 women-years) were diagnosed with probable dementia. The relative risk of probable dementia in the hormone therapy group was 2.05 (95% CI, 1.21 to 3.48) compared to placebo. Differences between groups became apparent in the first year of treatment. It is unknown whether these findings apply to younger postmenopausal women. (See BOXED WARNINGS, WARNINGS, Dementia, and PRECAUTIONS, Geriatric Use).

The estrogen-alone WHIMS substudy enrolled 2,947 predominantly healthy postmenopausal women 65 years of age and older (45 percent were age 65 to 69 years, 36 percent were 70 to 74 years, and 19 percent were 75 years of age and older) to evaluate the effects of CE.625 mg on the incidence of probable dementia (primary outcome) compared with placebo.

After an average follow-up of 5.2 years, 28 women in the estrogen alone group (37 per 10,000 women-years) and 19 in the placebo group (25 per 10,000 women-years) were diagnosed with probable dementia. The relative risk of probable dementia in the estrogen alone group was 1.49 (95% CI, 0.83 to 2.66) compared to placebo. It is unknown whether these findings apply to younger postmenopausal women. (See BOXED WARNINGS, WARNINGS, Dementia and PRECAUTIONS, Geriatric Use.)

INDICATIONS AND USAGE

In women with an intact uterus, Climara Pro is indicated in the:

1. Treatment of moderate to severe vasomotor symptoms associated with menopause.

2. Prevention of postmenopausal osteoporosis. When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis and non-estrogen medications should be carefully considered.
   The mainstays for decreasing the risk of postmenopausal osteoporosis are weight bearing exercise, adequate calcium and vitamin D intake, and when indicated, pharmacologic therapy. Postmenopausal women require an average of 1500mg/day of elemental calcium. Therefore, when not contraindicated, calcium supplementation may be helpful for women with suboptimal dietary intake. Vitamin D supplementation of 400-800 IU/day may also be required to ensure adequate daily intake in postmenopausal women. Risk factors for osteoporosis include low bone mineral density, low estrogen levels, family history of osteoporosis, previous fracture, small frame (low BMI), light skin color, smoking, and alcohol intake. Response to therapy can be predicted by pre-treatment serum estradiol, and can be assessed during treatment by measuring biochemical markers of bone formation/resorption, and/or bone mineral density.

CONTRAINDICATIONS

Climara Pro should not be used in women with any of the following conditions:

1. Undiagnosed abnormal genital bleeding.

2. Known, suspected, or history of cancer of the breast.

3. Known or suspected estrogen-dependent neoplasia.

4. Active deep vein thrombosis, pulmonary embolism or a history of these conditions.

5. Active or recent (e.g. within the past year) arterial thromboembolic disease (e.g., stroke, myocardial infarction).

6. Liver dysfunction or disease.

7. Known hypersensitivity to its ingredients of Climara Pro.

8. Known or suspected pregnancy. There is no indication for Climara Pro in pregnancy. There appears to be little or no increased risk of birth defects in children born to women who have used estrogens and progestins from oral contraceptives inadvertently during early pregnancy. (See PRECAUTIONS)

WARNINGS

See BOXED WARNINGS.

1. Cardiovascular disorders

Estrogen and estrogen/progestin therapy have been associated with an increased risk of cardiovascular events such as myocardial infarction and stroke, as well as venous thrombosis and pulmonary embolism (venous thromboembolism or VTE). Should any of these occur or be suspected, estrogens should be discontinued immediately.

Risk factors for arterial vascular disease (e.g., hypertension, diabetes mellitus, tobacco use, hypercholesterolemia, and obesity) and/or venous thromboembolism (e.g., personal history or family history of VTE, obesity, and systemic lupus erythematosus) should be managed appropriately.

a. Coronary heart disease and stroke
In the CE/MPA substudy of WHI an increased risk of CHD events (defined as nonfatal myocardial infarction and CHD death) was observed in women receiving CE/MPA compared to women receiving placebo (37 versus 30 per 10,000 women-years). The increase in risk was observed in year 1 and persisted. In the same substudy of WHI, an increased risk of stroke was observed in women receiving CE/MPA compared to women receiving placebo (29 versus 21 per 10,000 women-years). The increase in risk was observed after the first year and persisted. (See CLINICAL STUDIES.)

In the WHI estrogen-alone substudy, an increased risk of stroke was observed in women receiving CE compared to placebo (44 versus 32 per 10,000 women-years). The increase in risk was observed in year 1 and persisted.

In postmenopausal women with documented heart disease (n = 2,763, average age 66.7 years), a controlled clinical trial of secondary prevention of cardiovascular disease (Heart and Estrogen/Progestin Replacement Study; HERS) treatment with CE/MPA (0.625 mg/2.5 mg per day) demonstrated no cardiovascular benefit. During an average follow-up of 4.1 years, treatment with CE/MPA did not reduce the overall rate of CHD events in postmenopausal women with established coronary heart disease. There were more CHD events in the CE/MPA-treated group than in the placebo group in year 1, but not during the subsequent years. Participation in an open label extension of the original HERS trial (HERS II) was agreed to by 2,321 women. Average follow-up in HERS II was an additional 2.7 years, for a total of 6.8 years overall. Rates of CHD events were comparable among women in the CE/MPA group and the placebo group in HERS, HERS II, and overall.

b.Venous thromboembolism (VTE)
In the CE/MPA substudy of the WHI study, a 2-fold greater rate of VTE, including deep venous thrombosis and pulmonary embolism, was observed in women receiving CE/MPA compared to women receiving placebo. The rate of VTE was 34 per 10,000 women-years in the CE/MPA group compared to 16 per 10,000 women-years in the placebo group. The increase in VTE risk was observed during the first year and persisted. (See CLINICAL STUDIES)

In the WHI estrogen-alone substudy, an increased risk of deep vein thrombosis was observed in women receiving CE compared to placebo (21 versus 15 per 10,000 women-years). The increase in deep vein thrombosis risk was observed during the first year. (See CLINICAL STUDIES.)

If feasible, estrogens should be discontinued at least 4 to 6 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization.

2. Malignant neoplasms

a. Endometrial cancer
The use of unopposed estrogens in women with intact uteri has been associated with an increased risk of endometrial cancer. The reported endometrial cancer risk among unopposed estrogen users is about 2 to 12 times greater than in nonusers, and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with use of estrogens for less than one year. The greatest risk appears associated with prolonged use, with increased risks of 15- to 24-fold for 5 to 10 years or more. This risk has been shown to persist for at least 8 to 15 years after estrogen therapy is discontinued.

Clinical surveillance of all women taking estrogen/progestin combinations is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding. There is no evidence that the use of natural estrogens results in a different endometrial risk profile than synthetic estrogens of equivalent estrogen dose. Adding a progestin to estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer.

b. Breast cancer
The use of estrogens and progestins by postmenopausal women has been reported to increase the risk of breast cancer. The most important randomized clinical trial providing information about this issue is the CE/MPA substudy of the WHI study (see CLINICAL STUDIES). The results from observational studies are generally consistent with those of the WHI clinical trial and report no significant variation in the risk of breast cancer among different estrogens or progestins, doses, or routes of administration.

The CE/MPA substudy of WHI reported an increased risk of breast cancer in women who took CE/MPA for a mean follow-up of 5.6 years. Observational studies have also reported an increased risk for estrogen/progestin combination therapy, and a smaller increased risk for estrogen alone therapy, after several years of use. In the WHI trial and from observational studies, the excess risk increased with duration of use. From observational studies, the risk appeared to return to baseline in about 5 years after stopping treatment. In

addition, observational studies suggest that the risk of breast cancer was greater, and became apparent earlier, with estrogen/progestin combination therapy as compared to estrogen-alone therapy.

In the CE/MPA substudy, 26 percent of the women reported prior use of estrogen-alone and/or estrogen/progestin combination hormone therapy. After a mean follow-up of 5.6 years during the clinical trial, the overall relative risk of invasive breast cancer was 1.24 (95% confidence interval 1.01-1.54), and the overall absolute risk was 41 versus 33 cases per 10,000 women-years, for CE/MPA compared with placebo. Among women who reported prior use of hormone therapy, the relative risk of invasive breast cancer was 1.86, and the absolute risk was 46 versus 25 cases per 10,000 women-years, for CE/MPA compared with placebo. Among women who reported no prior use of hormone therapy, the relative risk of invasive breast cancer was 1.09, and the absolute risk was 40 versus 36 cases per 10,000 women-years for CE/MPA compared with placebo. In the same substudy, invasive breast cancers were larger and diagnosed at a more advanced stage in the CE/MPA group compared with the placebo group. Metastatic disease was rare with no apparent difference between the two groups. Other prognostic factors such as histologic subtype, grade and hormone receptor status did not differ between the groups.

The use of estrogen plus progestin has been reported to result in an increase in abnormal mammograms requiring further evaluation. All women should receive yearly breast examinations by a healthcare provider and perform monthly breast self-examinations. In addition, mammography examinations should be scheduled based on patient age, risk factors, and prior mammogram results.

3. Dementia
In the estrogen plus progestin WHIMS, a population of 4,532 postmenopausal women aged 65 to 79 years was randomized to CE/MPA or placebo. In the estrogen-alone WHIMS, a population of 2,947 hysterectomized women aged 65 to 79 years was randomized to CE or placebo.
In the estrogen plus progestin substudy, after an average follow-up of 4 years, 40 women being treated with CE/MPA (1.8 percent, n=2,229) and 21 women in the placebo group (0.9 percent, n=2,303) received diagnoses of probable dementia. The relative risk for CE/MPA versus placebo was 2.05 (95% confidence interval 1.21 - 3.48), and was similar for women with and without histories of menopausal hormone use before WHIMS. The absolute risk of probable dementia for CE/MPA versus placebo was 45 versus 22 cases per 10,000 women-years, and the absolute excess risk for CE/MPA was 23 cases per 10,000 women-years. It is unknown whether these findings apply to younger postmenopausal women. (See CLINICAL STUDIES and PRECAUTIONS, Geriatric Use.)
In the estrogen-alone substudy, after an average follow-up of 5.2 years, 28 women in the estrogen-alone group and 19 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for estrogen alone versus placebo was 1.49 (95 percent CI, 0.83-2.66). The absolute risk of probable dementia for estrogen alone versus placebo was 37 versus 25 cases per 10,000 women-years. It is unknown whether these findings apply to younger postmenopausal women. (See CLINICAL STUDIES and PRECAUTIONS, Geriatric Use)

4. Gallbladder disease
A 2- to 4-fold increase in the risk of gallbladder disease requiring surgery in postmenopausal women receiving estrogens has been reported.

5. Hypercalcemia
Estrogen administration may lead to severe hypercalcemia in patients with breast cancer and bone metastases. If hypercalcemia occurs, use of the drug should be stopped and appropriate measures taken to reduce the serum calcium level.

6. Visual abnormalities
Retinal vascular thrombosis has been reported in patients receiving estrogens. Discontinue medication pending examination if there is sudden partial or complete loss of vision, or a sudden onset of proptosis, diplopia, or migraine. If examination reveals papilledema or retinal vascular lesions, estrogens should be permanently discontinued.

PRECAUTIONS

A. General

1. Addition of a progestin when a woman has not had a hysterectomy
Studies of the addition of a progestin for 10 or more days of a cycle of estrogen administration, or daily with estrogen in a continuous regimen, have reported a lowered incidence of endometrial hyperplasia than would be induced by estrogen treatment alone. Endometrial hyperplasia may be a precursor to endometrial cancer.

There are, however, possible risks that may be associated with the use of progestins with estrogens compared to estrogen-alone regimens. These include a possible increased risk of breast cancer.

2. Elevated blood pressure
In a small number of case reports, substantial increases in blood pressure have been attributed to idiosyncratic reactions to estrogens. In a large, randomized, placebo-controlled clinical trial, a generalized effect of estrogens on blood pressure was not seen. Blood pressure should be monitored at regular intervals with estrogen use.

3. Hypertriglyceridemia
In patients with pre-existing hypertriglyceridemia, oral estrogen therapy may be associated with elevations of plasma triglycerides leading to pancreatitis and other complications.

4. Impaired liver function and past history of cholestatic jaundice
Estrogens may be poorly metabolized in patients with impaired liver function. For patients with a history of cholestatic jaundice associated with past estrogen use or with pregnancy, caution should be exercised and in the case of recurrence, medication should be discontinued.

5. Hypothyroidism
Estrogen administration leads to increased thyroid-binding globulin (TBG) levels. Patients with normal thyroid function can compensate for the increased TBG by making more thyroid hormone, thus maintaining free T_4 and T_3 serum concentrations in the normal range. Patients dependent on thyroid hormone replacement therapy who are also receiving estrogens may require increased doses of their thyroid replacement therapy. These patients should have their thyroid function monitored in order to maintain their free thyroid hormone levels in an acceptable range.

6. Fluid retention
Estrogen and estrogen/progestin therapy may cause some degree of fluid retention. Because of this, patients with conditions that might be influenced by this factor, such as a cardiac or renal dysfunction, warrant careful observation when estrogens are prescribed.

7. ***Hypocalcemia***
Estrogens should be used with caution in individuals with severe hypocalcemia.

8. Ovarian cancer
The CE/MPA sub-study of WHI reported that estrogen plus progestin increased the risk of ovarian cancer. After an average follow-up of 5.6 years, the relative risk for ovarian cancer for CE/MPA versus placebo was 1.58 (95% confidence interval 0.77- 3.24) but was not statistically significant. The absolute risk for CE/MPA versus placebo was 4.2 versus 2.7 cases per 10,000 women-years. In some epidemiological studies, the use of estrogen alone, in particular for ten or more years, has been associated with an increased risk of ovarian cancer. Other epidemiologic studies have not found these associations.

9. ***Exacerbation of endometriosis***
Endometriosis may be exacerbated with administration of estrogens.

10. ***Exacerbation of other conditions***
Estrogens may cause an exacerbation of asthma, diabetes mellitus, epilepsy, migraine or porphyria, systemic lupus erythematosus, and hepatic hemangiomas and should be used with caution in women with these conditions.

B. Information for Patients
Physicians are advised to discuss the Patient Information leaflet with patients for whom they prescribe Climara Pro.

C. Laboratory Tests
Estrogen administration should be initiated at the lowest dose for the approved indication and then guided by clinical response, rather than by serum hormone levels (e.g., estradiol, FSH).

D. Drug/laboratory Test Interactions
1. Accelerated prothrombin time, partial thromboplastin time, and platelet aggregation time; increased platelet count; increased factors II, VII antigen, VIII antigen, VIII coagulant activity, IX, X, XII, VII-X complex, II-VII-X complex, and beta-thromboglobulin; decreased levels of antifactor Xa and antithrombin III, decreased antithrombin III activity; increased levels of fibrinogen and fibrinogen activity; increased plasminogen antigen and activity.

2. Increased thyroid-binding globulin (TBG) levels leading to increased circulating total thyroid hormone levels as measured by protein-bound iodine (PBI), T_4 levels (by column or by radioimmunoassay) or T_3 levels by radioimmunoassay. T_3 resin uptake is decreased, reflecting the elevated TBG. Free T_4 and free T_3 concentrations are unaltered. Patients on thyroid replacement therapy may require higher doses of thyroid hormone.

3. Other binding proteins may be elevated in serum (i.e., corticosteroid binding globulin (CBG), sex hormone-binding globulin (SHBG)) leading to increased total circulating corticosteroids and sex steroids, respectively. Free hormone concentrations may be decreased. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-l-antitrypsin, ceruloplasmin).

4. Increased plasma HDL and HDL_2 cholesterol subfraction concentrations, reduced LDL cholesterol concentration, and in oral formulations increased triglycerides levels.

5. Impaired glucose tolerance.

6. Reduced response to metyrapone test.

E. Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term continuous administration of estrogen, with and without progestin, in women with and without a uterus, has shown an increased risk of endometrial cancer, breast cancer, and ovarian cancer. (See BOXED WARNINGS, WARNINGS and PRECAUTIONS.)

Long-term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, uterus, cervix, vagina, testis, and liver.

F. Pregnancy

Climara Pro should not be used during pregnancy. (See CONTRAINDICATIONS)

G. Nursing Mothers

Estrogen administration to nursing mothers has been shown to decrease the quantity and quality of the milk. Detectable amounts of estrogens and progestins have been identified in the milk of mothers receiving this drug. Caution should be exercised when Climara Pro is administered to a nursing woman.

H. Pediatric Use

Climara Pro is not indicated in children.

I. Geriatric Use

There have not been sufficient numbers of geriatric patients involved in studies utilizing Climara Pro to determine whether those over 65 years of age differ from younger subjects in their response to Climara Pro.

Of the total number of subjects in the estrogen plus progestin substudy of the WHI study, 44 percent (n = 7,320) were 65 years and older, while 6.6 percent (n = 1,095) were 75 years and older. There was a higher relative risk (CE/MPA versus placebo) of stroke and invasive breast cancer in women 75 and older compared to women less than 75 years of age.

In the estrogen plus progestin substudy of WHIMS, a population of 4,532 postmenopausal women, aged 65 to 70 years, was randomized to conjugated estrogens (CE 0.625 mg) plus medroxyprogesterone acetate (MPA 2.5 mg) or placebo. In the estrogen plus progestin group, after an average follow-up of 4 years, the relative risk (CE/MPA versus placebo) of probable dementia was 2.05 (95 percent CI, 1.21-3.48).

Of the total number of subjects in the estrogen-alone substudy of the WHI study, 46 percent (n = 4,943) were 65 years and older, while 7.1 percent (n = 767) were 75 years and older. There was a higher relative risk (CE versus placebo) of stroke in women less than 75 years of age compared to women 75 years and older.

In the estrogen-alone substudy of the WHIMS, a population of 2,947 hysterectomized women, aged 65 to 79 years, was randomized to estrogen alone (CE 0.625 mg) or placebo. In the estrogen-alone group, after an average follow-up of 5.2 years, the relative risk (CE versus placebo) of probable dementia was 1.49 (95 percent CI, 0.83-2.66).

Pooling the events in women receiving CE or CE/MPA in comparison to those in women on placebo, the overall relative risk of probable dementia was 1.76 (95 percent CI, 1.19-2.6). Since both substudies were conducted in women aged 65 to 79 years, it is unknown whether these findings apply to younger postmenopausal women. (See BOXED WARNINGS and WARNINGS, Dementia.)

ADVERSE REACTIONS

See BOXED WARNINGS, WARNINGS and PRECAUTIONS.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

Table 8: All Treatment Emergent Events Regardless of Relationship Reported at a Frequency of > 3% with Climara Pro in the 1 year Endometrial Hyperplasia Study

	Climara Pro 0.045 / 0.015 N* = 212	E_2 N = 204

Body as a whole		
Abdominal pain	9 (4.2)	11 (5.4)
Accidental Injury	7 (3.3)	6 (2.9)
Back pain	13 (6.1)	12 (5.9)
Flu syndrome	10 (4.7)	13 (6.4)
Infection	7 (3.3)	10 (4.9)
Pain	11 (5.2)	13 (6.4)
Cardiovascular		
Hypertension	7 (3.3)	9 (4.4)
Digestive		
Flatulence	8 (3.8)	11 (5.4)
Metabolic and Nutritional Disorders		
Edema	8 (3.8)	5 (2.5)
Weight gain	6 (2.8)	10 (4.9)
Musculoskeletal		
Arthralgia	9 (4.2)	10 (4.9)
Nervous		
Depression	12 (5.7)	7 (3.4)
Headache	11 (5.2)	14 (6.9)
Respiratory		
Bronchitis	9 (4.2)	7 (3.4)
Sinusitis	8 (3.8)	12 (5.9)
Upper Respiratory Infection	28 (13.2)	26 (12.7)
Skin and Appendages		
Application site reaction	86 (40.6)	69 (33.8)
Breast pain	40 (18.9)	20 (9.8)
Rash	5 (2.4)	10 (4.9)
Urogenital		
Urinary Tract Infection	7 (3.3)	8 (3.9)
Vaginal Bleeding	78 (36.8)	44 (21.6)
Vaginitis	4 (1.9)	6 (2.9)

*****N = total number of subjects in a treatment group; n = number of subjects with event

Irritation potential of Climara Pro was assessed in a 3-week irritation study. The study compared the irritation of a Climara Pro placebo patch (22 cm^2) to a Climara placebo (25 cm^2). Visual assessments of irritation were made on Day 7 of each wear period, approximately 30 minutes after patch removal using a 7-point scale (0 = no evidence of irritation; 1 = minimal erythema, barely perceptible; 2 = definite erythema, readily visible, or minimal edema, or minimal papular response; 3-7 = erythema and papules, edema, vesicles, strong extensive reaction).

The mean irritation scores were 0.13 (week 1), 0.12 (week 2), and 0.06 (week 3) for the Climara Pro placebo. The mean scores for the Climara placebo were 0.2 (week 1), 0.26 (week 2), 0.12 (week 3). There were no irritation scores greater than 2 at any timepoint in any subject.

In controlled clinical trials, withdrawals due to application site reactions occurred in 6 (2.1%) of subjects in the 12-week symptom study and in 71 (8.5%) of subjects in the 1-year endometrial protection study.

The following additional adverse reactions have been reported with estrogen and/or estrogen/progestin therapy:

1. Genitourinary system

Changes in vaginal bleeding pattern and abnormal withdrawal bleeding or flow; breakthrough bleeding; spotting; dysmenorrhea; increase in size of uterine leiomyomata; vaginitis, including vaginal candidiasis; change in amount of cervical secretion; changes in cervical ectropion; ovarian cancer; endometrial hyperplasia; endometrial cancer.

2. Breasts

Tenderness, enlargement, pain, nipple discharge, galactorrhea; fibrocystic breast changes; breast cancer.

3. Cardiovascular
Deep and superficial venous thrombosis; pulmonary embolism; thrombophlebitis; myocardial infarction; stroke; increase in blood pressure.
4. Gastrointestinal
Nausea, vomiting; abdominal cramps, bloating; cholestatic jaundice; increased incidence of gallbladder disease; pancreatitis; enlargement of hepatic hemangiomas.
5. Skin
Chloasma or melasma, which may persist when drug is discontinued; erythema multiforme; erythema nodosum; hemorrhagic eruption; loss of scalp hair; hirsutism; pruritus, rash.
6. Eyes
Retinal vascular thrombosis, intolerance to contact lenses.
7. Central nervous system
Headache; migraine; dizziness; mental depression; chorea; nervousness; mood disturbances; irritability; exacerbation of epilepsy, dementia.
8. Miscellaneous
Increase or decrease in weight; reduced carbohydrate tolerance; aggravation of porphyria; edema; arthalgias; leg cramps; changes in libido; urticaria, angioedema, anaphylactoid/anaphylactic reactions; hypocalcemia; exacerbation of asthma; increased triglycerides.

OVERDOSAGE
Serious ill effects have not been reported following acute ingestion of large doses of estrogen/progestin-containing oral contraceptives by young children. Overdosage of estrogen may cause nausea and vomiting, and withdrawal bleeding may occur in females.

DOSAGE AND ADMINISTRATION
When estrogen is prescribed for a postmenopausal woman with a uterus, a progestin should also be initiated to reduce the risk of endometrial cancer. A woman without a uterus does not need progestin. Use of estrogen, alone or in combination with a progestin, should be with the lowest effective dose and for the shortest duration consistent with treatment goals and risks for the individual woman. Patients should be re-evaluated periodically as clinically appropriate (e.g., 3-month to 6-month intervals) to determine if treatment is still necessary (see BOXED WARNINGS and WARNINGS) For women who have a uterus, adequate diagnostic measures, such as endometrial sampling, when indicated, should be undertaken to rule out malignancy in cases of undiagnosed persistent or recurring abnormal vaginal bleeding.
One Climara Pro transdermal system is available for use. Climara Pro delivers 0.045 mg of estradiol per day and 0.015 mg of levonorgestrel per day. The lowest effective dose of Climara Pro has not been determined.

Initiation of Therapy:
Women not currently using continuous estrogen or combination estrogen/progestin therapy may start therapy with Climara Pro at any time. However, women currently using continuous estrogen or combination estrogen/progestin therapy should complete the current cycle of therapy, before initiating Climara Pro therapy. Women often experience withdrawal bleeding at the completion of the cycle. The first day of this bleeding would be an appropriate time to begin Climara Pro therapy.

Therapeutic Regimen:
A Climara Pro 0.045 mg / 0.015 mg (22 sq cm) matrix transdermal system is worn continuously on the lower abdomen. A new system should be applied weekly during a 28-day cycle.

Application of the System:
Site Selection: Climara Pro should be placed on a smooth (fold free), clean, dry area of the skin on the lower abdomen. **Climara Pro should not be applied to or near the breasts**. The area selected should not be oily (which can impair adherence of the system), damaged, or irritated. The waistline should be avoided, since tight clothing may rub the system off or modify drug delivery. The sites of application must be rotated, with an interval of at least one week allowed between applications to the same site.
Application of the system: After opening the pouch, remove one side of the protective liner, taking care not to touch the adhesive part of the transdermal delivery system with the fingers. Immediately apply the transdermal delivery system to a smooth (fold free) area of skin on the lower abdomen. Remove the second side of the protective liner and press the system firmly in place with the hand for at least 10 seconds, making sure there is good contact, especially around the edges.
Care should be taken that the system does not become dislodged during bathing and other activities. If a system should fall off, the same system may be reapplied to another area of the lower abdomen. If necessary, a new transdermal system may be applied, in which case, the original treatment schedule should be continued. Only one system should be worn at any one time during one week dosing interval.
Once in place, the transdermal system should not be exposed to the sun for prolonged periods of time.

Removal of the System
Removal of the system should be done carefully and slowly to avoid irritation of the skin. Should any adhesive remain on the skin after removal of the system, allow the area to dry for 15 minutes. Then gently rubbing the area with an oil-based cream or lotion

should remove the adhesive residue. Used patches still contain some active hormones. Each patch should be carefully folded in half so that it sticks to itself before throwing it away.

HOW SUPPLIED

Climara Pro (Estradiol/Levonorgestrel Transdermal System) 0.045 mg/day estradiol and 0.015 mg/day levonorgestrel – each 22 cm_2 system contains 4.4 mg of estradiol and 1.39 mg of levonorgestrel. NDC 50419-491-04

Individual Carton of 4 systems

Storage Conditions:

Store at 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F) [See USP controlled Room Temperature].

Do not store unpouched.

Climara Pro Individual Carton

NDC 50419-491-04

4 systems

Climara Pro®

(Estradiol/Levonorgestrel Transdermal System)

0.045/0.015 mg/day

Contains 4.40 mg estradiol, USP and 1.39 mg levonorgestrel, USP per transdermal system. The remaining components of the system (acrylate copolymer adhesive, polyvinylpyrrolidone/vinyl acetate copolymer, polyethylene backing, and polyester release liner) are pharmacologically inactive.

Rx only

PATIENT INFORMATION

Updated November 16, 2005

Climara Pro®

(Estradiol/Levonorgestrel Transdermal System)

Read this Patient Information leaflet before you start taking Climara Pro and read what you get each time you refill Climara Pro. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

WHAT IS THE MOST IMPORTANT INFORMATION I SHOULD KNOW ABOUT CLIMARA PRO (COMBINATION OF ESTROGEN AND PROGESTIN HORMONES)?

- **Do not use estrogens with or without progestins to prevent heart disease, heart attacks, or strokes.**

Using estrogens and progestins may increase your chances of getting heart attacks, strokes, breast cancer, and blood clots.

- **Do not use estrogens with or without progestins to prevent dementia.**

Using estrogens with progestins may increase your risk of dementia.
You and your healthcare provider should talk regularly about whether you still need treatment with Climara Pro.

What is Climara Pro?
Climara Pro is a medicine that contains two kinds of hormones, estrogen and a progestin.
What is Climara Pro used for?
Climara Pro is used after menopause to:

- **reduce moderate to severe hot flashes.** Estrogens are hormones made by a woman's ovaries. The ovaries normally stop making estrogens when a woman is between 45 to 55 years old. This drop in body estrogen levels causes the "change of life" or menopause (the end of monthly menstrual periods). Sometimes, both ovaries are removed during an operation before natural menopause takes place. The sudden drop in estrogen levels causes "surgical menopause."
  When the estrogen levels begin dropping, some women develop very uncomfortable symptoms, such as feelings of warmth in the face, neck, and chest, or sudden strong feelings of heat and sweating ("hot flashes" or "hot flushes"). In some women, the symptoms are mild, and they will not need estrogens. In other women, symptoms can be more severe. You and your health care provider should talk regularly about whether you still need treatment with Climara Pro.

- **help reduce your chances of getting osteoporosis (thin weak bones)**. Osteoporosis from menopause is a thinning of the bones that makes them weaker and easier to break. If you use Climara Pro only to prevent osteoporosis from menopause, talk with your healthcare provider about whether a different treatment or medicine without estrogens might be better for you. You and your healthcare provider should talk regularly about whether you should continue with Climara Pro.
  Weight-bearing exercise, like walking or running, and taking calcium and vitamin D supplements may also lower your chances of getting postmenopausal osteoporosis. It is important to talk about exercise and supplements with your healthcare provider before starting them.

Who should not use Climara Pro?
Do not use Climara Pro if you have had your uterus removed (hysterectomy).
Climara Pro contains a progestin to decrease the chances of getting cancer of the uterus. If you do not have a uterus, you do not need a progestin and you should not use Climara Pro.
Do not start using Climara Pro if you:

- **have unusual vaginal bleeding**

- **currently have or have had certain cancers.** Estrogens may increase the chances of getting certain types of cancers, including cancer of the breast or uterus. If you have or had cancer, talk with your healthcare provider about whether you should use Climara Pro.

- **had a stroke or heart attack in the past year**

- **currently have or have had blood clots**.

- **currently have or have had liver problems**

- **are allergic to Climara Pro or any of its ingredients.** See the end of this leaflet for a list of ingredients in Climara Pro.

- **think you may be pregnant**
  Tell your health care provider:

- **if you are breastfeeding.** The hormones in Climara Pro can pass into your milk.

- **about all of your medical problems.** Your healthcare provider may need to check you more carefully if you have certain conditions, such as asthma (wheezing), epilepsy (seizures), migraine, endometriosis, lupus, problems with your heart, liver, thyroid, kidneys, or have high calcium levels in your blood.

- **about all the medicines you take,** including prescription and nonprescription medicines, vitamins, and herbal supplements. Some medicines may affect how Climara Pro works. Climara Pro may also affect how your other medicines work.

- **if you are going to have surgery or will be on bed rest.** You may need to stop using estrogens.

How should I use Climara Pro?
Climara Pro is a patch that you wear on your skin. The Climara Pro patch releases two hormones, estradiol and levonorgestrel. See the end of this leaflet for complete instructions on how to use Climara Pro.

1. Start at the lowest dose and talk to your healthcare provider about how well that dose is working for you.

2. Estrogens should be used at the lowest dose possible for your treatment only as long as needed. You and your healthcare provider should talk regularly (for example, every 3 to 6 months) about the dose you are using and whether you still need treatment with Climara Pro.

What are the possible side effects of estrogens?
Less common but serious side effects include:
- Breast cancer
- Cancer of the uterus
- Stroke
- Heart attack
- Blood clots
- Dementia
- Gallbladder disease
- Ovarian cancer

These are some of the warning signs of serious side effects:
- Breast lumps
- Unusual vaginal bleeding
- Dizziness and faintness
- Changes in speech
- Severe headaches
- Chest pain
- Shortness of breath
- Pains in your legs
- Changes in vision
- Vomiting

Call your healthcare provider right away if you get any of these warning signs, or any other unusual symptom that concerns you.
Common side effects include:
- Headache
- Breast pain
- Irregular vaginal bleeding or spotting

- Stomach/abdominal cramps, bloating
- Nausea and vomiting
- Hair loss

Other side effects include:
- High blood pressure
- Liver problems
- High blood sugar
- Fluid retention
- Enlargement of benign tumors of the uterus ("fibroids")
- Vaginal yeast infection

These are not all the possible side effects of Climara Pro. For more information, ask your healthcare provider or pharmacist.

What can I do to lower my chances of a serious side effect with Climara Pro?
- Talk with your healthcare provider regularly about whether you should continue using Climara Pro.
- See your healthcare provider right away if you get vaginal bleeding while using Climara Pro.
- Have a breast exam and mammogram (breast X-ray) every year unless your healthcare provider tells you something else. If members of your family have had breast cancer or if you have ever had breast lumps or an abnormal mammogram, you may need to have breast exams more often.
- If you have high blood pressure, high cholesterol (fat in the blood), diabetes, are overweight, or if you use tobacco, you may have higher chances for getting heart disease. Ask your healthcare provider for ways to lower your chances for getting heart disease.

Have an annual gynecologic exam

General information about safe and effective use of Climara Pro

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use Climara Pro for conditions for which it was not prescribed. Do not give Climara Pro to other people, even if they have the same symptoms you have. It may harm them.

Keep Climara Pro out of the reach of children.

This leaflet provides a summary of the most important information about Climara Pro. If you would like more information, talk with your healthcare provider or pharmacist. You can ask for information about Climara Pro that is written for health professionals. You can get more information by calling the toll free number (1-888-237-5394).

What are the ingredients in Climara Pro?

The active ingredients in Climara Pro are estradiol and levonorgestrel. Climara Pro also contains acrylate copolymer adhesive and polyvinylpyrrolidone/vinyl acetate copolymer.

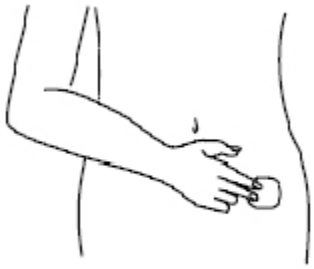
Do not store above 86°F (30°C).

Do not store unpouched.

Instructions for Use

How and Where do I apply the Climara Pro Patch
- Talk to your healthcare provider or pharmacist if you have questions about applying the Climara Pro patch.
- Each Climara Pro patch is individually sealed in a protective pouch. To open the pouch, hold it up with the Climara Pro name facing you. Tear left to right using the top tear notch. Tear from bottom to top using the side tear notch. Pull the pouch open. **Carefully remove the Climara Pro patch.** You will notice that the patch is attached to a thicker, hard-plastic liner and that the patch itself is oval.

- Apply the adhesive side of the Climara Pro patch to a clean, dry area of the lower abdomen. **Do not apply the Climara Pro patch to your breasts.** The sites of application must be rotated, with an interval of at least 1 week allowed between applications to a particular site. The area selected should not be oily, damaged, or irritated. Avoid the waistline, since tight clothing may rub and remove the patch. Application to areas where sitting would dislodge the patch should also be avoided. Apply the patch immediately after opening the pouch and removing the protective liner. Press the patch firmly in place with the fingers for about 10 seconds, making sure there is good contact, especially around the edges.



- The Climara Pro patch should be worn continuously for one week. You may wish to experiment with different locations when applying a new patch, to find ones that are most comfortable for you and where clothing will not rub on the patch.

- The Climara Pro patch should be changed once weekly. Remove the used patch. Carefully fold it in half so that it sticks to itself because used patches still contain active hormones and discard it. Any adhesive that might remain on your skin can be easily rubbed off. Then place the new Climara Pro patch on a different skin site. (The same skin site should not be used again for at least 1 week after removal of the patch.)

- Contact with water when you are bathing, swimming, or showering may affect the patch. If the patch falls off, the same patch may be reapplied to another area of the lower abdomen. Make sure that there is good contact, especially around the edges. If the patch will not stick completely to your skin, put a new patch on a different area of the lower abdomen. Do not apply two patches at the same time.

- Once in place, the transdermal system should not be exposed to the sun for prolonged periods of time.

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